Bevacizumab for the treatment of recurrent advanced ovarian cancer

ERRATUM

This report was commissioned by the NIHR HTA Programme as project number 11/40

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the manufacturer's factual inaccuracy check.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
10	Last sentence has been amended to reflect that IRC-determined analyses are sensitivity and exploratory analyses.
11	Second paragraph has been amended to reflect that IRC-determined analyses are sensitivity and exploratory analyses.
13	The word "sensitivity" has been deleted from the first sentence of the last paragraph.
29	Text amended to reflect that there are two trials evaluating bevacizumab in the first-line treatment of ovarian cancer.
48	Text amended so as not to suggest that ICON7 is the only trial evaluating bevacizumab in the first-line treatment of ovarian cancer.
54	Text in first paragraph of Section 4.2 amended to reflect that IRC-determined analyses are sensitivity and exploratory analyses.
59	The word "exploratory" has been substituted for "sensitivity" in the sentence describing the IRC-determined objective response rate.
76	Text in Section 4.4.1 (bullet point 7) amended to reflect that IRC-determined analyses are sensitivity and exploratory analyses.
153	The word "sensitivity" has been deleted from the last line.

recurrent platinum-sensitive ovarian cancer. The ERG's clinical expert fed back that paclitaxel plus carboplatin would be the preferred treatment in the UK for patients with recurrent platinum-sensitive ovarian cancer, particularly for patients who relapse >12 months after completion of first-line chemotherapy. At this time, PLDH is unavailable in the UK. Expert opinion is that use of PLDH plus carboplatin in the treatment of recurrent platinum-sensitive ovarian cancer is likely to increase when PLDH becomes available once again. The manufacturer carried out a systematic review of the literature to identify studies that could potentially inform a network meta-analysis (NMA). In addition to the OCEANS trial, the manufacturer identified publications on three other large trials in recurrent platinum-sensitive ovarian cancer that evaluated regimens listed as comparators of interest in the scope. After evaluating the trials and seeking statistical advice on the feasibility of an indirect comparison, the manufacturer decided against carrying out an NMA. However, the ERG considers that an NMA could have been attempted.

1.2 Summary of clinical effectiveness evidence submitted by the manufacturer

The OCEANS trial was a US-based multicentre, double-blind, parallel-group study that included 484 patients with first-recurrence of platinum-sensitive ovarian cancer. Bevacizumab was given initially as a concurrent treatment added to gemcitabine plus carboplatin. After completion of gemcitabine plus carboplatin cycles (maximum of 10 cycles), treatment with bevacizumab was maintained until disease progression or unacceptable toxicity, whichever occurred first. Bevacizumab was administered intravenously at a dose of 15 mg/kg on day 1 of each cycle, before administration of gemcitabine plus carboplatin.

Investigator-assessed progression-free survival (PFS) was the primary outcome evaluated in OCEANS, with PFS defined as the time from random assignment to disease progression (investigator-determined) or death from any cause. Addition of bevacizumab to gemcitabine plus carboplatin was associated with a statistically significant increase in the duration of PFS compared with placebo (Hazard ratio [HR] 0.48; 95% CI: 0.39 to 0.61; p <0.0001). Median duration of PFS was 12.4 months in the bevacizumab group compared with 8.4 months in the placebo group. The manufacturer proposes that strategies that extend duration of PFS, thereby prolonging the platinum-free interval, are important for improving patient outcomes and prognosis in subsequent lines of treatment.

Secondary outcomes evaluated in OCEANS were overall survival (OS), investigator-assessed objective response rate (ORR), and median duration of objective response. Sensitivity and exploratory analyses included analyses based on evaluation of PFS (sensitivity), ORR (exploratory), and median duration of response (exploratory) by an independent-review committee (IRC).

ORR was defined as the occurrence of a complete or partial response, and was confirmed by a repeat assessment performed ≥4 weeks after the criteria for response were first met. Based on investigator-assessed ORR, a statistically significant larger proportion of patients achieved an objective response with bevacizumab compared with placebo (190/242 [78.5%] in the bevacizumab group vs 139/242 [57.4%] in the placebo group; p <0.0001). In addition, the proportion of patients achieving a complete response was larger with bevacizumab (42/242 [17.4%] with bevacizumab vs 22/242 [9.1%] with placebo; statistical significance not reported). Of the patients achieving objective response, those in the bevacizumab group had a longer investigator-assessed median duration of response compared with those in the placebo group (10.4 months with bevacizumab group vs 7.4 months with placebo), with a 47% reduction in the risk of disease progression compared with placebo (HR 0.53; 95% CI: 0.41 to 0.67; p <0.0001).

The results of the sensitivity analysis for PFS, and exploratory analyses of ORR and median duration of response, carried out by the IRC seem to support the results of the assessments of the OCEANS investigators.

Within the submitted evidence, the manufacturer presents data from three interim analyses of OS. At the time of writing, OS data from OCEANS are immature. None of the interim analysis found a statistically significant difference between the addition of bevacizumab and the addition of placebo in duration of OS. The direction of effect in the first interim analysis favoured bevacizumab (25% reduction in risk of mortality; HR 0.75; 95% CI: 0.53 to 1.05). The mean effect size generated from the second and third interim analyses approached 1, that is, there was no difference between bevacizumab and placebo in the duration of OS. Moreover, the manufacturer argues that OS data are confounded as a result of administration of bevacizumab post-progression to the placebo group. At the time of the second interim analysis of OS, the manufacturer estimates that 34.7% of patients in the placebo group had received bevacizumab post-progression compared with 18.1% of patients in the bevacizumab group. The ERG agrees with the manufacturer that administration of bevacizumab post-progression is a confounding factor in determination of OS and asserts that confounding of OS data is a well-recognised complexity in clinical trials evaluating treatments for cancer.

The Summary of Product Characteristics (SmPC) for bevacizumab indicates that the most frequently observed adverse effects with bevacizumab are hypertension, fatigue or asthenia, diarrhoea and abdominal pain. Patients with a history of hypertension are at risk of developing proteinuria. In the submitted evidence, a larger proportion of patients in the bevacizumab group experienced an adverse event compared with the placebo group, including various Grade 3 and Grade 4 events, and adverse events of special interest (AESIs). Hypertension, proteinuria, epistaxis, and headache were the adverse effects for which the most substantial difference (>10%) in occurrence was observed between the bevacizumab and placebo groups. In addition, hypertension and proteinuria were two of the AESIs occurring with ≥2% higher incidence in the bevacizumab group compared with the placebo group.

1.4 ERG commentary on the robustness of evidence submitted by the manufacturer

1.4.1 Strengths

Clinical

The ERG considers the OCEANS RCT to be a well-designed trial, and considers the results of the submitted evidence to be relevant to the decision problem that is the focus of this STA.

To be eligible for enrolment in OCEANS, patients were required to have first-recurrence of platinum-sensitive ovarian cancer; patients receiving prior chemotherapy in the recurrent setting were excluded. Thus, in terms of number of previous chemotherapeutic treatments, OCEANS includes a clinically homogeneous population.

Economic

The ERG notes that the modelling approach adopted by the manufacturer was reasonable and consistent with previous economic evaluations in recurrent ovarian cancer. The ERG notes that the model was generally well constructed and transparent, although the ERG identified a number of minor errors within the model, and several inconsistencies between the numbers reported in the manufacturer's submission and the model.

1.4.2 Weaknesses

Clinical

Submitted evidence is based on one RCT, which provides direct evidence for only the comparison of adding bevacizumab versus adding placebo to gemcitabine and carboplatin. There is no direct evidence available evaluating the clinical effectiveness of bevacizumab in combination with platinum-based chemotherapy (monotherapy or combination therapy) compared with other platinum-based chemotherapy used in UK clinical practice to treat first-recurrence of platinum-sensitive ovarian cancer. OCEANS allowed patients to receive a maximum of 10 cycles of chemotherapy. Clinical practice in the UK is to administer a maximum of 6 cycles of chemotherapy. There is no evidence to suggest that additional cycles of chemotherapy are associated with increased benefit.

The ERG has concerns around the transparency and consistency in the reporting of the results from the analyses based on IRC-determined PFS, ORR, and median duration of response. Within the MS, the manufacturer fully reported data and statistical analyses for the primary analysis of PFS and other investigator-assessed outcomes. By contrast, reporting of corresponding absolute data and results of statistical significance tests for sensitivity analyses was incomplete. The manufacturer was unable to provide all absolute values requested during clarification, indicating that "these data do not appear to be reported in the OCEANS CSR or elsewhere in the relevant publications". Based on the

evaluating bevacizumab in the treatment of recurrent ovarian cancer, the ERG considers the restriction of the intervention to be appropriate. In addition, as noted in Section 2.2, the positive opinion issued by the CHMP focuses on the use of bevacizumab in combination with gemcitabine plus carboplatin,[27] and thus, as the manufacturer highlights, the licence for bevacizumab is likely to be granted for use in combination only with gemcitabine and carboplatin.

The manufacturer identifies that bevacizumab was first approved by the US Food and Drug Administration (FDA) in 2004 for use in metastatic colorectal cancer in combination with standard chemotherapy. In 2005, bevacizumab was launched in the UK. Since its introduction to the market, bevacizumab has been licensed in the European Union (EU) for use in various cancers in combination with standard chemotherapy regimens:[31]

- metastatic cancer of the colon or rectum (large intestine);
- metastatic breast cancer;
- advanced, metastatic or recurrent non-small cell lung cancer that cannot be removed by surgery alone in patients whose cancer cells are not of the 'squamous' type;
- advanced or metastatic kidney cancer;
- advanced EOC, FTC, and PPC (first-line treatment; not recurrent disease).

Bevacizumab is also licensed in numerous countries outside of the EU for the treatment of relapsed glioblastoma.

Bevacizumab is a humanised monoclonal antibody that inhibits vascular endothelial growth factor (VEGF), and is the first licensed anti-VEGF targeted therapy in ovarian cancer. VEGF is a signal protein that is important in the signalling cascade that stimulates the growth of new blood vessels (angiogenesis).[10] As noted in Section 2.1, angiogenesis has been identified as having an important role in tumour growth and metastasis. VEGF receptors are predominantly expressed by endothelial cells, and VEGF has been found to be produced by several types of tumour, including ovarian tumours. By blocking VEGF-induced signalling, bevacizumab inhibits VEGF-driven angiogenesis, thus reducing vascularisation of tumours and inhibiting tumour growth.

The Summary of Product Characteristics (SmPC) for bevacizumab reports that, in ovarian cancer, the recommended dose of bevacizumab is 15 mg/kg of body weight, given once every 3 weeks as an intravenous infusion.[32] In the first-line treatment of advanced ovarian cancer, the SmPC reports that bevacizumab has been given in addition to carboplatin and paclitaxel for up to 6 cycles of treatment, after which bevacizumab is continued as a single agent until disease progression, or for a maximum of 15 months, or until unacceptable toxicity, whichever occurs first. The ERG considers it important to note that, in one of two trials evaluating the effectiveness of bevacizumab in the first-line treatment of advanced ovarian cancer (ICON7), bevacizumab was administered at a dose of 7.5 mg/kg of body

(PFS). The protocol allowed unblinding at progression of disease, and, therefore, investigators and patients may have been unblinded to treatment allocation at the time of investigator-assessed disease progression. The ERG is satisfied that OCEANS was adequately blinded.

Intervention

Bevacizumab (or placebo) was administered intravenously on day 1 of each cycle before gemcitabine plus carboplatin at a dose of 15 mg/kg of body weight, which is the recommended dose of bevacizumab when used in combination with paclitaxel plus carboplatin in the first-line treatment of advanced ovarian cancer (FIGO stages IIIB, IIIC and IV).[32] As noted earlier, in ICON7, which evaluated the effectiveness of bevacizumab in the first-line treatment of advanced ovarian cancer, bevacizumab was administered at a dose of 7.5 mg/kg of body weight.[33] After completion of gemcitabine plus carboplatin, bevacizumab (or placebo) was continued at the same dose as a monotherapy until either disease progression or unacceptable toxicity, whichever occurred first. Gemcitabine (1,000 mg/m^2 on days 1 and 8) and carboplatin (area under the curve [AUC] 4 on day 1) were given intravenously for 6–10 cycles. Cycles were repeated every 21 days. Treatment on day 1 of each cycle was held if the absolute neutrophil count was <1,500/μL, haemoglobin was <8.5 g/dL, or platelet count was <100,000/μL within 24 hours of scheduled treatment. Cycles could be delayed for a maximum of 3 weeks until these values were achieved. Bevacizumab or placebo could be held for up to 3 weeks if carboplatin and gemcitabine were held, to allow for administration of study drug on the same day as administration of gemcitabine and carboplatin. In addition, bevacizumab or placebo could be held for toxicity for a maximum of 6 weeks to allow recovery; the trial protocol specified that cessation of treatment for longer than 6 weeks required the discontinuation of bevacizumab. Should a component of therapy be discontinued because of toxicity, the patient was eligible to continue with the other components per protocol.

OCEANS was designed such that patients would receive six cycles of gemcitabine plus carboplatin but, if the assessing investigator deemed it necessary, and the study Sponsor approved, patients could receive up to 10 cycles.[28] It has been reported that the number of cycles of chemotherapy does not influence median OS but longer durations of chemotherapy are associated with greater toxicity compared with shorter durations.[23] At this time, there is consensus that patients should receive a maximum of six cycles of chemotherapy.[23] The ERG's clinical expert indicated that more than six cycles of chemotherapy is unlikely to be given in UK clinical practice as there is no evidence to indicate that a higher number of cycles is associated with an increase in clinical benefit. Although patients could receive up to a maximum of 10 cycles, data presented within the MS indicate that the mean number of cycles (based on the safety evaluable population) received was about six cycles each of gemcitabine and carboplatin (summarised in Table 9). However, as a percentage, ~50% of patients received 4–6 cycles of gemcitabine and of carboplatin. Of the remaining patients, ~40% received 7–

4.2 Summary of submitted evidence

As discussed earlier, the primary efficacy outcome of OCEANS was investigator-assessed PFS based on RECIST criteria.[28] Secondary outcomes analysed were OS, ORR, and median duration of objective response. Sensitivity analyses included an evaluation of PFS by an IRC and analysis of PFS that included patients who received non-protocol therapies. Exploratory analyses were evaluation of ORR and median duration of response by the IRC. Within the MS, the manufacturer fully reported data and statistical analyses for the primary analysis of PFS and other investigator-assessed outcomes. By contrast, reporting of corresponding absolute data and results of statistical significance tests for sensitivity analyses was incomplete. The inconsistent reporting of data and analyses in the MS prompted the ERG to request the CSR for OCEANS as part of the clarification process. The manufacturer was unable to provide the full CSR, and instead made available a copy of the report used when preparing the submission, adding that "while the core report refers to additional sections, these were not available prior to submission of the MS and are not provided in this version". Individual outcomes and the manufacturer's responses are discussed separately in the sections that follow.

4.2.1 Summary of results on clinical effectiveness

Primary outcome: progression-free survival

Addition of bevacizumab to gemcitabine and carboplatin was associated with a statistically significant increase in duration of PFS compared with addition of placebo (HR 0.48; 95% CI: 0.39 to 0.61; p <0.0001): summary of PFS analysis is presented in Table 10 and the Kaplan–Meier analysis for the primary outcome is provided in Appendix 4. Median duration of PFS was 12.4 months in the bevacizumab group compared with 8.4 months in the placebo group. The manufacturer proposes that strategies that extend duration of PFS, thereby prolonging the platinum-free interval, are important for improving patient outcomes and prognosis in subsequent lines of treatment.

For completeness, during clarification, the ERG asked the manufacturer to provide the mean duration of PFS in each group based on analyses of data at clinical cut-off. The manufacturer did not provide the mean PFS, stating that the analysis of PFS was conducted before all patients had progressed, and, therefore, the maximum PFS value is unknown and a mean cannot be calculated. The ERG acknowledges that not all patients had progressed, but asserts that the reported analysis is likely to be the sole analysis of PFS and a mean duration based on the data collected could have been provided.

The IRC-determined sensitivity analysis supports the findings of the investigator-assessed result for PFS, with median durations of PFS of 12.3 months and 8.6 months for the bevacizumab and placebo groups, respectively (HR 0.45; 95% CI: 0.35 to 0.58; Table 10); Kaplan–Meier analysis of IRC-determined PFS is presented in Appendix 5.

The ERG agrees with the manufacturer that confounding due to post-progression treatment is a well-recognised difficulty associated with interpretation of OS data, but considers that this issue is common to trials evaluating cancer treatments, as highlighted in FDA guidance.[39]

Table 1. Interim analyses of overall survival

OS	Bevacizumab (N = 242)	Placebo (N = 242)
First interim OS analysis[a]		
Number (%) of patients with an event	63 (26.0)	78 (32.2)
Median overall survival (months) (95% CI)	35.5 (30.0 to not estimable)	29.9 (26.4 to not estimable)
HR (relative to placebo) (95% CI)	**0.75 (0.53 to 1.05)**	
Second interim OS analysis[a]		
Number (%) of patients with an event	123 (50.8)	112 (46.3)
Median overall survival (months) (95% CI)	33.3 (29.8 to 35.5)	35.2 (29.9 to 40.3)
HR (relative to placebo) (95% CI)	**1.03 (0.79 to 1.33)**	
Third interim OS analysis[a]		
Number (%) of patients with an event	144 (59.5)	142 (58.7)
Median overall survival (months) (95% CI)	33.4 (30.3 to 35.8)	33.7 (29.3 to 38.7)
HR (relative to placebo) (95% CI)	**0.96 (0.76 to 1.21)[b]**	

[a] First patient was enrolled on 17th April 2007. Cut-off dates for analyses were: first interim analysis = 17th September 2010 (final progression-free survival analysis); second interim analysis = 29th August 2011; and third interim analysis (carried out at the request of the European Medicines Agency) = 30th March 2012.

[b] HR reported in the manufacturer's submission to be relative to placebo. However, the quoted HR is for placebo relative to bevacizumab.[50]

Abbreviations used in table: CI, confidence interval; HR, hazard ratio; OS, overall survival.

Objective response rate and duration of response

ORR was defined as the occurrence of a complete or partial response, and was confirmed by a repeat assessment performed ≥4 weeks after the criteria for response were first met; criteria for response were assessed based on the modified RECIST criteria (presented in Table 4).

In investigator-assessed ORR, a statistically significant larger proportion of patients achieved an objective response with bevacizumab compared with placebo (190/242 [78.5%] in the bevacizumab group vs 139/242 [57.4%] in the placebo group; p<0.0001); results summarised in Table 12. In addition, the proportion of patients achieving a complete response was larger with bevacizumab (42/242 [17.4%] with bevacizumab vs 22/242 [9.1%] with placebo; statistical significance not reported). The results of the exploratory analysis for ORR carried out by the IRC are in agreement with the results of the investigator-assessed analysis (summarised in Table 12). The ERG notes that the proportion of patients classified as achieving an objective response is comparable for the investigator-

4.4 Conclusions of the clinical effectiveness section

4.4.1 Clinical results

- The submitted evidence is derived from the OCEANS trial.[28]
- OCEANS assessed the effects of adding bevacizumab versus adding placebo to gemcitabine plus carboplatin for the treatment of first-recurrence of platinum-sensitive ovarian cancer. In terms of number of previous chemotherapeutic treatments, OCEANS includes a clinically homogeneous population.
- Bevacizumab does not have a European licence at this time for use in recurrent ovarian cancer. However, the CHMP has issued a positive opinion on the use of bevacizumab in combination with gemcitabine plus carboplatin for the treatment of patients with first-recurrence of platinum-sensitive ovarian cancer who have not received prior therapy with a VEGF inhibitor or VEGF receptor-targeted agent.[27]
- In the investigator-assessed analysis, addition of bevacizumab was associated with a statistically significant improvement in the primary outcome of PFS (HR 0.48; 95% CI: 0.39 to 0.61).
- The manufacturer proposes that strategies that extend the duration of PFS during second-line treatment will improve treatment outcome and maintain the platinum-sensitivity of patients, thereby improving patient outcomes and prognosis in subsequent lines of treatment.
- Secondary outcomes assessed were OS, ORR, and median duration of response. Bevacizumab was associated with statistically significant improvements across all outcomes.
- Sensitivity analysis included an independent analysis of PFS by an IRC, and an analysis including patients censored for receipt of non-protocol specified therapies. Exploratory analyses included analysis of ORR and duration of response by the IRC. Based on data presented within the MS, the IRC analyses support the investigator-assessed analyses, generating similar results for PFS, ORR and median duration of response.
- At the time of writing this report, OS data from OCEANS are immature. The manufacturer has carried out three interim analyses for OS, all of which found no significant difference between bevacizumab and placebo. Moreover, the HR for the second and third analyses approached 1, indicating no difference in effect between treatments.
- Adverse effects associated with bevacizumab were hypertension and proteinuria, both of which are recognised adverse effects of treatment. Bevacizumab has been reported to increase the risk of gastrointestinal perforation. However, during OCEANS, no cases of gastrointestinal perforation were reported in either group.
- Exploratory NMA carried out by the ERG for the outcome of PFS found that bevacizumab plus gemcitabine and carboplatin is statistically significantly more effective at improving PFS compared with NICE recommended platinum-based chemotherapy regimens.

4.4.2 Clinical issues

- Only one RCT is available for the comparison of adding bevacizumab versus adding placebo to gemcitabine and carboplatin. In addition, this is the only direct comparison reported.
- OCEANS allowed patients to receive a maximum of 10 cycles of chemotherapy. The ERG's clinical expert indicated that patients in the UK are likely to receive a maximum of 6 cycles of chemotherapy. Within OCEANS, ~40% of patients received between 7 and 10 cycles of chemotherapy. The ERG is unclear as to whether the additional cycles of chemotherapy are likely to have an impact on the overall results.
- The reporting of the results from the IRC is not transparent.

outlined in the positive opinion, and which it is anticipated that the licence will stipulate, is relevant to the scope issued by NICE.

The submitted direct evidence addresses only one comparison of interest outlined in the NICE scope. In terms of indirect evidence, the manufacturer identified three large trials that could potentially be used to construct a network meta-analysis (NMA). The manufacturer decided against carrying out an NMA. After independently evaluating the RCTs identified by the manufacturer, and obtaining clinical advice, the ERG considers that the identified trials were sufficiently comparable to inform an NMA. The ERG undertook an exploratory analysis, the results of which suggest that addition of bevacizumab to gemcitabine and carboplatin prolongs duration of PFS compared with all chemotherapeutic regimens listed as comparators of interest in the final scope. For example, bevacizumab added to gemcitabine and carboplatin was associated with a reduction in risk of progression or death from any cause of 53% compared with paclitaxel plus carboplatin (HR 0.47; 95% Credible Interval [CrI]: 0.33 to 0.66) and of 42% compared with PLDH plus carboplatin (HR 0.58; 95% CrI: 0.39 to 0.82). The ERG stresses that its analyses are speculative and, as such, should be interpreted with caution.

With regards to the manufacturer's systematic reviews, the ERG has some reservations around the methods implemented. Abstracts were appraised by only one reviewer and the manufacturer specified an inclusion criterion that trials should include a minimum of 200 patients. The ERG suggests that these restrictions limit the robustness of the manufacturer's systematic reviews. However, the ERG acknowledges that the manufacturer has likely identified all studies evaluating bevacizumab in the treatment of first recurrence of platinum-sensitive ovarian cancer. By contrast, the ERG notes that RCTs that could potentially inform an NMA were excluded at appraisal stage. Due to time constraints, the ERG was unable to replicate the manufacturer's review of the literature to inform an NMA, and considers that there may be additional relevant studies not reported in the manufacturer's submission (MS).

Within the MS, several inconsistencies and omissions were noted in the reporting of various analyses and number of events. Inconsistent reporting of data was also prominent in the manufacturer's response to the ERG's requests for clarification. In particular, the number of patients discontinuing due to an adverse effect remains unclear. Importantly, during clarification, the manufacturer was unable to confirm the number of patients lost to follow-up at the time of final PFS analysis, or to provide a mean PFS. In addition, the numbers of patients censored at the time of final PFS analysis and at the time of the three interim OS analyses are unclear. Although reasons for censoring of patients are described in full in the MS, no details on the number of patients censored in each analysis are reported in either the MS or the full publication of OCEANS. The ERG also has concerns around the transparency and consistency in the reporting of the results from the analyses based on